REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor

Critical limb ischemia

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Critical limb ischemia (CLI) continues to be a significantly morbid disease process for the aging population. Rigid guidelines for the management of patients with CLI are inappropriate due to the complexities that are involved in optimally treating these patients. A thin line exists in the decision process between medical management vs surgical management by revascularization or amputation, and the perception of "success" in this patient population is evolving. This review explores these issues and examines the challenges the treating physician will face when managing the care of patients with CLI. The epidemiology and natural history of CLI is discussed, along with the pathophysiology of the disease process. A review of the literature in regards to the different treatment modalities is presented to help the physician optimize therapy for patients with CLI. New scoring systems to help predict outcomes in patients with CLI undergoing revascularization or amputation are discussed, and an overview of the current status of patient-oriented outcomes is provided. Finally, we briefly examine emerging therapies for the treatment of CLI and provide an algorithm to help guide the practicing physician on how to approach the critically ischemic limb with regard to the complicated issues surrounding these patients. (J Vasc Surg 2010;51:230-41.)

Critical limb ischemia is defined as limb pain that occurs at rest, or impending limb loss that is caused by severe compromise of blood flow to the affected extremity.[1] Although the hallmark of peripheral arterial occlusive disease is an issue of supply vs demand, that is, inadequate blood flow to supply vital oxygen demanded by the limb, critical limb ischemia (CLI) occurs after chronic lack of blood supply, setting off a cascade of pathophysiologic events that ultimately lead to rest pain or trophic lesions of the legs, or both.[2] Thus, CLI is considered the "end stage" of peripheral arterial disease (PAD).

The international consensus on the definition of CLI is the following: any patient with chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven arterial occlusive disease.[3] CLI is not to be confused with acute occlusion of the distal arterial tree, but rather a disease process that occurs in a chronic setting of months to years and, if left untreated, ultimately leads to limb loss secondary to lack of adequate blood flow and oxygenation through the distal extremities. Given that CLI is a severe manifestation of PAD, these patients would be classified in the more severe ends of the Fontaine classification (stage III-IV) or the Rutherford classification (grades 4-6; Table I).

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Recent evidence, however, suggests that CLI does not always progress though the various stages of these classification systems.[4] In fact, a multicenter prospective study looking at amputations in patients with ischemia found that more than half of their cohort did not have any PAD symptoms 6 months before onset of CLI.[5] Because this study was not limited to only CLI patients, but any patient with ischemia requiring amputation, one cannot extrapolate that CLI mainly manifests in asymptomatic patients rather than through the Fontaine or Rutherford classifications. Yet, these studies highlight that CLI progression from PAD is variable and unpredictable and can circumvent the traditional understanding of the progression from PAD to CLI.

Regardless of where in the spectrum of PAD these patients fit, it can be agreed that CLI patients suffer from the worst form of PAD, and approaches to maximize early detection and optimize surgical and nonsurgical therapies should be high priority in the medical forum. Patients with CLI experience significant morbidity, with cardiovascular event rates surpassing those in patients with symptomatic coronary artery disease (CAD).[6]

Rates of amputations in the general population with PAD are declining, but amputations continue to be performed despite recent advances in revascularization, partly because patients with CLI are referred to vascular surgeons late in their course, but perhaps more importantly, because there is no agreed upon definition of a non-salvageable limb.[7,8] Bear in mind that most of the data that do exist focus on a physician-oriented view of success: graft patency, limb salvage, and survival.[9] Only in the past few years has patient-oriented outcomes research garnered attention, and limb amputation may actually improve quality of life

Table I. Classification schemes of peripheral arterial disease

Classification	*Stage*	*Clinical description*
Fontaine	I	Asymptomatic
	IIa	Mild claudication
	IIb	Moderate-to-severe claudication
	III	Rest pain
	IV	Ulceration or gangrene
Rutherford	0	Asymptomatic
	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
	4	Rest pain
	5	Minor tissue loss
	6	Severe tissue loss or gangrene

(QOL) compared with limb salvage in select patient populations.

The diagnosis of CLI is straightforward because of the vascular examination, the ankle-brachial index (ABI), and a number of imaging modalities, but how to optimally care for patients with CLI, whether surgically or medically, is not as clear. This review will explore these issues and provide insight into the optimal clinical management of patients with CLI.

EPIDEMIOLOGY AND NATURAL HISTORY

PAD affects 8 to 10 million Americans and is associated with a threefold to sixfold increased risk of cardiovascular morbidity and death compared with individuals without PAD.[10] PAD patients are at an exceptionally high risk for cardiovascular events and most eventually die of a cardiac or cerebrovascular event.[11] Patients with CLI also have a greater risk of sustaining cardiovascular ischemic events than those with PAD alone.[1] Patients with CLI represent approximately 1% of the total number of patients with PAD, with overall mortality in these patients approaching 50% at 5 years and 70% at 10 years.[12-14] Immediate postoperative mortality and major limb amputation is also considerable, with a recent meta-analysis reviewing 31 studies involving bypass grafts for CLI showing rates as high as 11.6%.[15] A study in 2009 revealed amputation rates at 1 year after lower extremity bypass of 12% for patients with CLI vs 1% for patients with claudication.[16]

The recent multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery (PREVENT III) confers, arguably, the best data for CLI patients undergoing vein bypass grafting, because it studied strictly CLI patients and included patients with advanced comorbidities or those requiring complex operative procedures. A 2.7% perioperative mortality rate, 5.2% graft occlusion rate, 16% mortality rate at 1 year, 80% secondary patency rate at 1 year, and an 88% limb salvage rate at 1 year was observed.[17]

Demonstrating that the diagnosis of CLI has remained a predictor of poor overall survival and outcomes during the past decade, and that these rates have not changed substantially, Bertele et al[18] reported in 1999 a large prospective observational multicenter cohort consisting of 1586 patients with CLI and observed a 6-month amputation rate of 12% and 1-year mortality rate of 19.1%. In fact, several observational studies of patients diagnosed with CLI reveal that at 1 year, only 50% of the patients will remain amputation-free, although they may still be symptomatic, whereas 25% will require a major amputation. The remaining 25% will have died.[3] These numbers may be underestimated, because many patients with CLI are lost to follow-up.

The economic burden of CLI is considerable. Brahmanandam et al[19] recently reported that patients with CLI undergoing revascularization used more health care services after hospital discharge than non-CLI patients. These services included home health care and transfers to rehabilitation facilities. The authors reported that independent predictors for increased health care services utilization included older age, female gender, care at a private hospital, longer length of hospitalization, African American race, highest income quartile, and undergoing amputation or débridement.[19] The cost of clinical care for patients with CLI in 1990 was estimated at $43,000/patient-year.[20] The mean cost of inpatient hospital treatment during the first 12 months of follow-up in patients undergoing surgical bypass for CLI was estimated at £23,322 sterling, which was approximately one-third higher than patients undergoing angioplasty treatment.[21]

Others have shown that although there is nearly a twofold difference in initial cost, the cost-savings of endovascular therapy is not realized over time secondary to subsequent reintervention, particularly in CLI patients.[22] Finally, the median cost of managing a patient after amputation is estimated at almost twice that of successful limb salvage.[23] Thus, CLI represents a challenging disease state that is associated with considerable morbidity and mortality, in addition to a large financial impact on society.

PATHOPHYSIOLOGY

CLI is usually caused by obstructive atherosclerotic disease; however, CLI can also be caused by atheroembolic or thromboembolic disease, vasculitis, in situ thrombosis related to hypercoagulable states, thromboangiitis obliterans, cystic adventitial disease, popliteal entrapment, or trauma.[1] Regardless of the etiology, the pathophysiology of CLI is a chronic and complex process that affects the macrovascular and microvascular systems, as well as surrounding tissues (Table II).

Initially, the body response to ischemia is angiogenesis, or capillary sprouting, as well as arteriogenesis, thereby promoting the enlargement of pre-existing collaterals to aid in the increase of blood flow to the critically ischemic limb.[24,25] These responses fail to supply the necessary amount of blood flow and oxygen to the limb, causing arterioles in patients with CLI to become maximally vasodilated and insensitive to provasodilatory stimuli.[25] This phenomenon, referred to as vasomotor paralysis, is thought to be the result of chronic exposure to vasorelaxing factors

Table II. Pathophysiology of critical limb ischemia

Macrovascular changes	*Microvascular changes*
Atherosclerosis	Decreased nitric oxide production
Arterial stenosis	Increased reactive oxygen species
Angiogenesis	Increased peroxynitrite production
Arteriogenesis	Increased platelet activation
Increased VEGF	Increased leukocyte adhesion
Increased SDF-1	Microvascular thrombosis
Increased CXCR4 expression	Precapillary arteriole collapse
Vasomotor paralysis	Impaired oxygen exchange
Arterial remodeling	
Decreased wall thickness	
Decreased cross-sectional area	
Decreased wall-to-lumen ratio	
Increased skin perfusion	
Edema	

CXCR4, CXC chemokine receptor; *SDF-1,* stromal cell-derived factor-1; *VEGF,* vascular endothelial cell factor.

in patients with diseased vessels.[25] Further, blood vessels in patients with CLI have decreased wall thickness, decreased cross-sectional area, and decreased wall-to-lumen ratio compared with controls.[25]

Together, these changes lead to edema, a major concern in these patients. In addition, patients with CLI often hold their limbs in a dependent position to alleviate ischemic rest pain; combined with impaired vasomotor control, this leads to further aggravation of the edema. Edema increases the hydrostatic pressure within the distal portion of the limb, compressing already compromised capillaries and impairing diffusion of nutrients to the tissue.[25]

To complicate matters, microvascular dysfunction occurs in addition to the macrovascular changes. The endothelium protects the integrity of the blood vessel by modulating vascular tone, controlling vascular permeability, and acting as an antithrombogenic barrier. Chronic ischemia from macroscopic disease leads to alterations in structure and function of endothelial cells and alterations in pressure unloading, which results in microcirculatory adaptations. This endothelial dysfunction leads to microthrombosis within the capillaries and exacerbates edema formation in the extremity.[25] Furthermore, endothelial trauma results in increased free radical production, inappropriate platelet activation, and leukocyte adhesion, all of which lead to microthrombi formation.[25] The end result is that tissue oxygen exchange at the capillary level is impeded and less effective.

Many patients greatly benefit from restoration of flow, which is required for wound healing and limb salvage to occur. Yet simply reinstating blood flow on a macrovascular level alone will not reverse the derangements discussed above. In fact, doing so initiates reactive hyperemia and a cascade of events that may further exacerbate an already complex problem.[25] Thus, treatment of CLI must take into consideration a multitude of factors on a case-by-case basis to sort out the optimal course of action: medical management, revascularization, or amputation.

TREATMENT

The diagnosis of CLI cannot be stressed enough, given the high morbidity and mortality associated with the disease process. Although CLI is a clinical diagnosis, it should be confirmed objectively and early in the disease process through ABI, toe systolic pressures, or transcutaneous partial pressure of oxygen ($TcPO_2$). Once the diagnosis is confirmed, the goals of treating CLI are to relieve ischemic pain, heal ischemic ulcers, prevent limb loss, improve patient function and QOL, and prolong survival. Revascularization could optimally achieve these goals, but the severity of comorbidities, along with durability of the reconstruction in patients with CLI, demands a risk-benefit analysis to determine the optimal therapy. Modification of risk factors to curb the progression of CLI have not been well studied in this patient population, but it would be extremely prudent that the same risk factor management that is undertaken in patients with cardiovascular disease be optimized in all patients who present with PAD and CLI. Once this has been undertaken, the role of medical vs surgical therapy can then be assessed.

Nonsurgical management. Some patients who present to vascular surgeons for surgical or endovascular procedures are poor candidates for surgical or endovascular procedures because of medical comorbidities, nonambulatory status, or poor outflow vessels in the limb, thus limiting revascularization as a viable option. Further, data are currently sparse regarding which patients should definitively be treated with early amputation.

Marston et al[26] reported a subset of patients who satisfied the TransAtlantic Intersociety Consensus (TASC) criteria for CLI and presented with extensive but uncomplicated and stable tissue loss, but could not undergo revascularization due to comorbidities or anatomic considerations that did not allow revascularization without acceptable risk. A surrogate for the natural history of CLI was thus examined in patients managed nonoperatively and treated with a dedicated wound management plan only. The primary outcome revealed that only 38% of patients required limb amputation at 1 year; however, ulcer healing was slow, with only 25% healed at 6 months and slightly more than 50% healed at 1 year.[26]

The group also evaluated the ability of noninvasive diagnostic tools to predict the probability of limb loss and found that an ABI <0.5 was a significant predictor of limb loss, although ABIs were obtained in only half the limbs studied. Neither ankle nor toe pressures were predictive of limb loss or wound closure. Thus, for the subset of patients who are poor surgical candidates with stable tissue loss and favorable ABIs, conservative management with dedicated long-term wound care may be sufficient for limb salvage.

Various reports have demonstrated that cardioprotective medications such as statins, antihypertensive medications, and antiplatelet agents are associated with a decreased cardiovascular event rate in patients with PAD.[27]

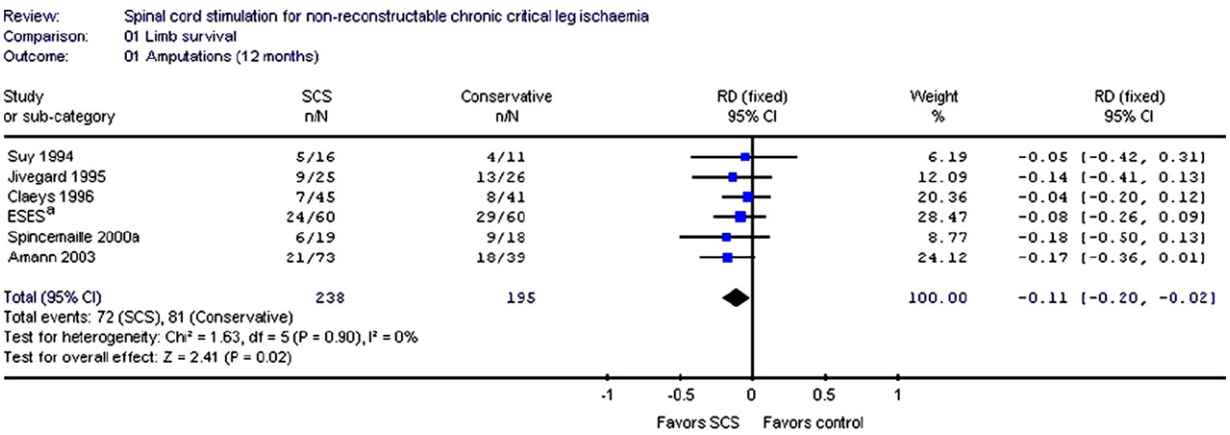

Fig 1. Meta-analysis of 12-month amputation rates in patients with critical limb ischemia from six studies comparing spinal cord stimulation *(SCS)* vs medical management. *CI,* confidence interval; *RD,* risk difference. (Reprinted from *Journal of Pain and Symptom Management*, 31/4 Suppl. Ubbink DT, Vermeulen H. Spinal cord stimulation for critical leg ischemia. S32, 2006, with permission from Elsevier.[35])

However, little is known about the effectiveness of these drugs in the patient population at greatest risk—patients with CLI—because these studies have been performed in heterogenous populations. Schanzer et al[28] used the PREVENT III cohort to shed light on this. In this cohort, 45% were taking statins, 59% were taking β-blockers, and 80% were taking antiplatelet therapy. Only statin use was associated with improved survival in CLI patients 1 year after revascularization, whereas β-blockers and antiplatelet medication had no effect on survival. Of note, hypertriglyceridemia independently increased the risk for progression of intermittent claudication to CLI,[29] but no published study to date has examined the effect of treating hypertriglyceridemia in the natural history of CLI.

In patients with CLI, progression to gangrene occurs in 40% of diabetic patients compared with 9% of nondiabetic patients.[30] Further, limb salvage rates in diabetic patients with CLI have been reported to be lower than nondiabetic patients, and diabetes is an independent risk factor for postoperative amputation and complications in CLI.[31] A recent a prospective, randomized controlled trial in type 2 diabetic patients with established macrovascular disease examined the effect of pioglitazone, a synthetic ligand for the peroxisome proliferator-activated receptor that when activated alters the transcription of genes to improve insulin sensitivity. Treatment with pioglitazone reduced the composite of all-cause mortality, nonfatal myocardial infarction, and stroke, but had no significant effect on the rate of leg revascularization or amputation.[32]

The natural history of patients with CLI treated with certain pharmacologic agents has also been studied. Placebo-controlled studies have evaluated the use of iloprost, a prostacyclin analogue, for CLI. Norgren et al[33] reported an average 43.5% incidence of limb loss in the placebo group, with no significant difference in the iloprost group at 6 months.[33] Similarly, Brass et al[34] showed that lipo-ecraprost failed to modify the 6-month amputation rate in patients with CLI who were not candidates for revascularization.[34] Thus, prostacyclin analogues have no role in the management of CLI at this time.

Spinal cord stimulation has been proposed as an alternative to amputation in patients with CLI and severe pain. It involves the implantation of stimulation electrodes at the level of L3-L4 and a subcutaneous pulse generator. A recent meta-analysis of randomized controlled studies showed a modest positive effect of spinal cord stimulation in CLI patients in terms of pain relief, as well as an 11% reduction in amputation rate compared with optimal medical treatment at 12 months (Fig 1). The authors concluded these positive benefits of spinal cord stimulation should be weighed against the high cost and possible complications from this therapy.[35]

In summary, risk factors and comorbidities for PAD and cardiovascular disease should be identified and controlled. Statin therapy has been shown to improve survival in patients with CLI and should be considered for these patients. Spinal cord stimulation may have a role in pain management for patients with CLI, but the risks must be weighed against the benefits. Dedicated wound regimens can increase limb salvage rates in certain patients who are unable to tolerate an operation, but most patients are better served with revascularization or amputation, if amenable to surgical intervention.

Surgical management: revascularization or primary amputation. For patients able to tolerate surgical procedures, revascularization, including bypass surgery, with or without thromboendarterectomy, as well as endovascular techniques offers the best chance for limb salvage. Overall, in CLI patients undergoing infrainguinal bypass, a recent meta-analysis revealed that the 5-year primary graft patency is 63%, secondary patency is 71%, and limb salvage is 78%.[15] These results may lack generalizability, however, because these data reflect only a subgroup of vascular centers specializing in the management of CLI.[36] This is further

Table III. Meta-analysis of 1-month to 3-year patency, limb salvage, and patient survival in patients with critical limb ischemia comparing percutaneous transluminal angioplasty vs bypass grafting[a]

Result	*1 month*	*6 months*	*1 year*	*2 years*	*3 years*
Primary patency					
PTA	77.4 ± 4.1	65.0 ± 7.0	58.1 ± 4.6	51.3 ± 6.6	48.6 ± 8.0
Bypass	93.3 ± 1.1	85.8 ± 2.1	81.5 ± 2.0	76.8 ± 2.3	72.3 ± 2.7
P	<.05	<.05	<.05	<.05	<.05
Secondary patency					
PTA	83.3 ± 1.4	73.8 ± 7.1	68.2 ± 5.9	63.5 ± 8.1	62.9 ± 11.0
Bypass	94.9 ± 1.0	89.3 ± 1.6	85.9 ± 1.9	81.6 ± 2.3	76.7 ± 2.9
P	<.05	<.05	<.05		
Limb salvage					
PTA	93.4 ± 2.3	88.2 ± 4.4	86.0 ± 2.7	83.8 ± 3.3	82.4 ± 3.4
Bypass	95.1 ± 1.2	90.9 ± 1.9	88.5 ± 2.2	85.2 ± 2.5	82.3 ± 3.0
Patient survival					
PTA	98.3 ± 0.7	92.3 ± 5.5	87.0 ± 2.1	74.3 ± 3.7	68.4 ± 5.5
Bypass	NA	NA	NA	NA	NA

NA, Not applicable; *PTA,* percutaneous transluminal angioplasty.
[a]Reprinted from *Journal of Vascular Surgery*, Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. 47(5) 975-981, 2008, with permission from Elsevier.[40]

evidenced by Chung et al,[37] who showed a 25% wound complication rate in CLI patients undergoing infrainguinal bypass with reversed saphenous vein, with primary patency rates of 63% and 50% at 1 and 3 years, respectively, and limb salvage rates of 85% and 79%.

Although there is debate whether emerging endovascular treatment is preferable to open surgery, the general consensus is that bypass surgery is preferable to angioplasty in patients with a TASC D lesion.[38] Further, those who favor surgery usually emphasize good long-term anatomic patency and clinical durability. However, this preference could come at the cost of high morbidity and mortality as well as substantial resource utilization.[36]

The multicenter, prospective, randomized, double-blinded PREVENT III trial has provided important insights into patients with CLI. PREVENT III was designed to determine the efficacy of edifoligide, a molecule that inhibits the expression of genes that stimulate vascular smooth muscle cell proliferation, in preventing autogenous vein graft failure in CLI patients undergoing infrainguinal bypass grafting.[17] The primary study end point was the time to occurrence of nontechnical index graft failure resulting in graft revision or major amputation ≤12 months. Secondary end points included all-cause graft failure, clinically significant graft stenosis, amputation or reintervention-free survival, and nontechnical primary graft patency.

The results showed no significant difference between the treatment groups in the primary or secondary trial end points, primary graft patency, or limb salvage. However, the PREVENT III cohort was analyzed for disparity in race and gender on outcomes,[39] and black race and female gender were risk factors for inferior graft patency and limb salvage outcomes. Further, the combination of female gender and black race had synergistic negative effects, with black women at highest risk for graft failure and limb loss. Notably, perioperative and 1-year mortality rates were similar in all groups.

The Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) study was a multicenter, randomized controlled trial that set out to compare the outcomes of a strategy of bypass surgery first vs angioplasty first in patients presenting with CLI due to infrainguinal disease.[21] When examined in the medium term, the rates of amputation-free survival, all-cause mortality, and health-related QOL were similar in both groups, although more morbidity was incurred and hospital costs were one-third higher ≤1 year in the surgery-first group. Yet, the surgery-first patients who remained alive with an intact limb for >2 years had a prolonged subsequent life compared with the angioplasty group. Vessel or graft patency rates were not reported for this trial.

A recent meta-analysis that reviewed infrapopliteal angioplasty in CLI patients was compared with a similar meta-analysis of popliteal-distal vein bypass grafts in a similar patient population (Table III).[40,41] The authors concluded that given the equivalent limb salvage rates between the two surgical modalities, percutaneous transluminal angioplasty (PTA) remains a viable option in treating CLI patients, although additional studies should be conducted to examine this further.

Recently, Conte et al[42] developed objective performance goals to define appropriate outcome measures for CLI trials. They pooled data from three prospective multicenter trials of open surgical revascularization for CLI (ie, PREVENT III, Circulase II, and BASIL) and found that the combination of age >80 years and tissue loss was associated with a 3.1-fold increased risk of major adverse cardiac events. Furthermore, these two parameters were associated with inferior outcomes for all end points that included death. Use of a high-risk conduit (nonsaphenous, spliced, or small-caliber vein) and an infrapopliteal location for outflow were associated with worse limb-related end points. Thus, as more trials are designed to determine the

role of new devices for treating patients with CLI, the patients can be risk stratified more appropriately.

The aforementioned studies comparing surgical and endovascular revascularization included diabetic patients within the cohort; however, a recent single-center prospective cohort study examined the efficacy of PTA or bypass surgery as first-line treatment for CLI in patients with and without diabetes.[43] Diabetic patients with CLI benefitted from revascularization regardless of the modality chosen, although multiple revascularization procedures may be required. Further, the mortality and amputation-free survival were similar to the diabetic cohort in the BASIL trial.

While advances in open and endovascular techniques continue to be made, amputations continue to be performed, with overall incidence rates approaching nearly two major amputations per 10,000 individuals with PAD performed annually in the United States.[7] In fact, TASC has identified indications for patients with CLI who would benefit from primary amputation: unreconstructable arterial occlusive disease, necrosis of significant areas of the weight-bearing portion of the foot, a fixed and irremediable flexion contracture of the leg, a terminal illness, or a very limited life expectancy because of comorbid conditions.[12] Further, amputation may offer an expedient return to a useful QOL.

A recent prospective study by Abou-Zamzam et al[44] examined factors leading to primary amputation vs revascularization. During a 4-year period, 224 patients underwent surgery for CLI, with 43% undergoing primary amputation and 57% undergoing revascularization. Univariate analysis showed nonwhite ethnicity, diabetes mellitus, end-stage renal disease, major tissue loss, dependent living situation, and nonambulatory status were independent predictors of amputation vs revascularization. The group found that system-related factors, such as time to vascular surgery evaluation, did not influence treatment. The authors implied limb salvage could be improved by aggressive treatment of medical comorbidities to prevent late complications of CLI along with earlier recognition of tissue loss.

We must point out that most series comparing perioperative mortality or long-term survival in CLI have favored revascularization rather than amputation overall.[45] Yet, these are not randomized trials, and given the increased comorbidities in patients receiving primary amputations, if patients were to be randomized to revascularization or amputation, the mortality and long-term survival rates would likely be improved in the amputation groups. Still, current data that are available favor revascularization when feasible in terms of overall mortality.

PREDICTIVE INDICES

That CLI is a poor surrogate for survival has been well established. CAD has been estimated to be present in >50% of patients with CLI.[46,47] Criqui et al[10] evaluated 10-year mortality rates in patients with PAD and found the relative risk of dying among those with large vessel PAD vs no PAD was 3.1 for death from all causes and 5.9 for all deaths from cardiovascular disease.[10] Further, death due to cardiovascular disease was 15-fold higher among symptomatic individuals with severe PAD.

Although not specific to CLI patients, the Veterans Affairs National Surgical Quality Improvement Program (NSQIP) cohort showed that PAD patients receiving dialysis, and not patients with milder degrees of renal insufficiency, are at higher risk for limb loss after revascularization compared with patients with normal renal function, and that dialysis-dependent renal failure was the most significant determinant of amputation-free survival.[48] In a study examining patients with claudication or CLI, a similar poor amputation-free survival was observed for patients receiving dialysis.[49] In the same NSQIP cohort, patients with only moderate renal insufficiency were less likely to receive a revascularization procedure for CLI than those with normal renal function, but the risk for death was lower among patients with moderate renal insufficiency who underwent arterial reconstruction than among those who underwent amputation or no intervention.[50] For those patients with diabetes and advanced PAD, mortality rates were higher whereas limb salvage rates were lower.[51,52]

Given the cardiovascular burden and significant comorbidities that add to the already complicated decision-making process, a risk assessment method to predict poor outcome in patients with CLI undergoing surgical revascularization could more accurately stratify which patients are most at risk for postoperative death or major limb amputation, or both. Biancari et al,[53] from the national vascular registry in Finland (Finnvasc), developed such a risk-scoring method to better predict immediate postoperative outcome after femoral endarterectomy, femoropopliteal bypass, or infrapopliteal bypass surgery in patients with CLI.[53]

Using the Finnvasc registry with data on 3925 infrainguinal surgical revascularization procedures, they found in the overall series that 30-day postoperative mortality and major amputation rates were 3.1% and 6.3%, respectively. The 30-day postoperative mortality and/or limb-loss rate was 9.2%. Numerous risk factors were included in the analysis, including CAD, cerebrovascular accident, and renal disease, but multivariate analysis showed that only diabetes, CAD, foot gangrene, and urgent operation were independent risk factors of death or limb loss, or both. A risk score was developed by assigning 1 point each to these risk factors (Fig 2). Predictive correlation was observed between patients with higher risk scores and 30-day rates of postoperative mortality or major amputation.

Although in its infancy, this bedside risk-scoring system appears to provide meaningful information to the clinician that may aid in the decision process when contemplating surgical revascularization in a patient with CLI. Of note, in the Finnvasc risk scoring method of predicting outcome, renal failure was assessed and was not an independent risk factor of death or limb loss, or both, but patients requiring dialysis were not differentiated from renal failure.

Schanzer et al[54] recently developed a model to predict amputation-free survival using the PREVENT III cohort. Five independent predictors of amputation-free survival were identified from the cohort and a risk score was as-

Risk Factor	Points
Diabetes mellitus	1
Coronary artery disease	1
Foot gangrene	1
Urgent operation	1

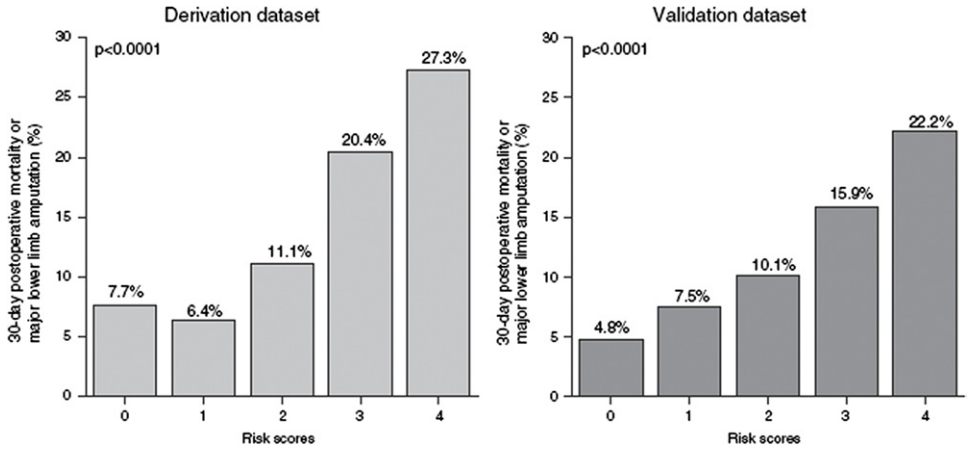

Fig 2. FINNVASC risk stratification of critical limb ischemia. Four independent risk factors of mortality and/or limb loss were identified, and 30-day mortality and limb amputation risk are shown for both the derivation and validation data sets. (With kind permission from Springer Science+Business Media: *World Journal of Surgery,* Risk-scoring method for prediction of 30-day postoperative outcome after infrainguinal surgical revascularization for critical lower-limb ischemia: a Finnvasc registry study, 31, 2007, p 222, Biancari F, Salenius JP, Heikkinen M, Luther M, Ylonen K, Lepantalo M.[53])

signed to each: dialysis-dependent renal failure, 4 points; tissue loss, defined as nonhealing ulcer or gangrene, 3 points; age ≥75 years, 2 points; a hematocrit <30%, 2 points; and a history of advanced CAD, 1 point. The derivatization and validation model were able to predict that the 1-year amputation-free survival rate was 86% for patients with ≤3 points (low risk), 73% for patients with 4 to 7 points (medium risk), and 45% for patients with ≥8 points when undergoing revascularization with vein bypass grafting. The authors stated that diabetes was not an independent predictor of amputation-free survival, given that when dialysis and tissue loss were incorporated into the model, the association between diabetes and amputation-free survival was attenuated and no longer significant.[54] This risk score has recently been validated both internally and externally with three independent cohorts in 3286 patients with CLI.[55]

Goodney et al[16] looked at the ability to predict preoperatively which patients will be ambulatory 1 year after lower extremity bypass, with 75% of the patients in this study diagnosed with CLI as the indication for operative intervention. Age, preoperative ambulatory ability, independent living status, CLI, graft patency, and amputation were predictors of ambulation at 1 year. Furthermore, patients with none of these risk factors had a <5% risk of death or nonambulatory status at 1 year, whereas patients with three or more risk factors had a 50% risk of death or nonambulatory status at 1 year.

Recently, Tang et al[56] developed a vascular biochemistry and hematology outcomes model (VBHOM) to predict death after limb amputation in patients with CLI that uses data items that can be obtained preoperatively and are available from all patients (Table IV). The group developed this binary logistic regression model by examining patients retrospectively for an 8-year period and applied it prospectively to a second separate validation set of patients. The VBHOM equation includes gender, mode of admission, age on admission, urea, sodium, potassium, hemoglobin, white cell count, creatinine, and urea/creatinine. When applied to the 269 patients in the validation set, the mean predicted mortality was 32%, or 85 deaths, and the actual mortality was 85 deaths. Thus, the VBHMO appears to provide a model that can adequately predict death after limb amputation in patients with CLI.

Given that CLI patients have complex comorbidities that vary from patient to patient, adoption of rigid guidelines to determine which patients should be offered surgical intervention would be ill advised. However, the predictive indices that have been discussed can help guide this often-difficult decision-making process by presenting data that can predict morbidity and death depending on patient risk factors at 30 days and up to 1 year. Thus a more objective decision can be made by both the physician and patient in terms of how to proceed in the management of CLI on an individualized basis.

Table IV. Vascular biochemistry and hematology outcomes model (VBHOM) in patients with critical limb ischemia[a]

VBHOM variables					
Gender					
Mode of admission					
Age of admission					
Urea, mmol/L					
Sodium, mmol/L					
Potassium, mmol/L					
Hemoglobin, g/dL					
White cell count, $\times 10^9$					
Creatinine, mmol/L					
Urea/creatinine					
VBHOM model to validation set[b]					
% Range predicted mortality	*No.*	*Mean % predicted risk*	*Predicted deaths*	*Reported deaths*	χ^2
0.0-20.1	77	12.11	9	11	0.34
20.1-27.5	39	24.02	9	8	0.26
27.5-32.9	31	30.20	9	15	4.87
32.9-37.7	27	35.02	9	9	0.03
37.7-41.4	21	39.29	8	6	1.01
41.4-45	18	42.95	8	9	0.37
45-49	17	46.64	8	8	0.00
49-55	15	51.72	8	4	3.77
55-64	14	59.70	8	9	0.12
64-100	10	72.72	7	6	0.82
0-100	269	31.53	85	85	11.60

$\chi^2 = 11.60$, 10 df, $P = .313$; no evidence of lack of fit; C-index – 0.677.
[a]The variables accounted for in the equation are shown, as well as the mortality results of the prospective application of the VBHOM model to the validation set.
[b]Reprinted from *European Journal of Vascular and Endovascular Surgery*, Tang TY, Prytherch DR, Walsh SR, Athanassoglou V, Seppi V, Sadat U, et al. The development of a VBHOM-based outcome model for lower limb amputation performed for critical ischaemia, 37(1) 62-66, 2009, with permission from Elsevier.[56]

PATIENT-ORIENTED OUTCOMES

Although a moderate amount of data are available on the physician-oriented view of success in patients with CLI, including graft patency, limb salvage, and survival, patient-oriented outcomes are now coming to the forefront. In fact, the TASC consortium has stated there are no QOL instruments that have been standardized in a large population of patients with CLI and has identified this as a "critical issue."[12] This may be because patients are often not clinically stable, the treatments offered to these patients involve significant morbidity, or the outcomes for this end-of-life population are complex.[13] If the physician approaches the treatment of patients with CLI in a more patient-focused manner, rather than the current lesion-focused manner, subgroups of the CLI population undergoing extensive limb salvage may be better off with primary amputation or nonoperative management.

Abou-Zamzam et al[57] evaluated patient-oriented outcomes in a retrospective study of the preoperative and postoperative living situation and ambulatory status in CLI patients undergoing lower extremity bypass. At 6 months, 99% of patients who were living independently and 97% of patients who were ambulatory preoperatively maintained these outcomes. Yet, only 4% of patients who were in a dependent living situation preoperatively went on to live independently at 6 months, and only 21% who did not ambulate preoperatively were independently ambulatory 6 months after surgery. Multivariate analysis confirmed preoperative living situation and ambulatory status as predictors of outcome at 6 months postoperatively.

A subsequent study by Nicoloff et al[58] monitored similar patients for 42 months and found that with longer follow-up, there was greater decline in independent ambulation and living status postoperatively. Further, only 14% of patients had an uncomplicated operation, relief of symptoms, complete wound healing, no need for reoperation, and maintenance of functional status. The remaining 86% spent a major portion of their remaining lives undergoing treatment for CLI.

Taylor et al[51] evaluated functional outcomes at 5 years for surgical revascularization procedures. For living members of this cohort, 70.6% maintained ambulation postoperatively and 81.3% continued to live independently. Significant determinants of poor functional outcome included impaired ambulatory ability at the time of presentation and the presence of dementia. Location or type of reconstruction as well as comorbidities did not predict functional outcomes.

Finally, Crawford et al[59] examined 30-day outcomes from the NSQIP database and showed that dependent functional status was an independent predictor of major complications and death after surgical bypass grafting. When dependent functional status was combined with an emergency presentation, the odds of a major complication were increased fivefold, and the odds of death were increased 38-fold. Dependent status combined with hemodialysis was associated with a 13-fold increase in death. Dependent status combined with age >80 years was associated with an 87-fold increase in death. Thus, foregoing revascularization may be prudent when these factors are present.

Even with the paucity of retrospective data for functional outcomes in patients with CLI, the amount of prospective data in terms of QOL is lacking even further, and data that are available involves mainly patient questionnaires. The Short-Form 36 (SF-36) Health Survey and Nottingham Health Profile (NHP) have been most widely used in patients with PAD, but to date there is no consensus on the ideal questionnaire to evaluate patients with CLI.[60]

The largest study performed to date that prospectively analyzed patient QOL after surgical revascularization was the PREVENT III trial, comprising 1404 patients.[17,61] Significant improvements in QOL were identified in patients undergoing surgical revascularization at 3 and 12 months compared with baseline, and factors associated with failure of QOL improvement included diabetes and graft-related events. Of note, questionnaires were com-

Table V. Emerging therapies for critical limb ischemia

First author	*Classification*	*No.*	*Modality*	*Outcome*
Baumgartner[63]	CLI (tissue loss or rest pain)	9	Gene therapy (VEGF165)	Improvement in ABI from 0.33 to >.048; ischemic ulcers healed or markedly improved in 4 of 7 limbs; limb salvage in 3 patients initially planned for BKA
Rajagopalan[64]	PAD (exercise-limiting intermittent claudication)	105	Gene therapy (VEGF165)	No difference in peak walking time, ABI, claudication onset time, or quality of life
Powell[65]	CLI (rest pain or tissue loss)	104	Gene therapy (HGF)	Increase in $TcPO_2$ in high-dose group; no difference in rate of amputation, wound healing, or ABI
Nikol[66]	CLI (tissue loss)	125	Gene therapy (FGF-1)	No difference in ulcer healing; twofold risk reduction of all and major amputations
Tateishi-Yuyama[67]	CLI (rest pain, tissue loss)	47	Cell therapy (BM-MNC)	Improvement in ABI, $TcPO_2$, and rest pain, and pain-free walking time
Huang[68]	CLI (diabetic patients with rest pain or tissue loss)	28	Cell therapy (G-CSF mobilized PB-MNC)	Improvement in pain-free walking distance, diabetic foot ulcers, ABI, and angiographic scores.
Lenk[69]	CLI and PAD	7	Cell therapy (CPC)	Increase in pain-free walking distance, ABI, $TcPO_2$, flow-dependent vasodilation, flow response in response to adenosine, endothelium-dependent vasodilation

ABI, Ankle-brachial index; *BKA,* below-knee amputation; *BM-MNC,* bone marrow-mononuclear cells; *CLI,* critical limb ischemia; *CPC,* circulating blood-derived progenitor cells; *FGF,* fibroblast growth factor; *G-CSF,* granulocyte colony-stimulating factor; *HGF,* hepatocyte growth factor; *PAD,* peripheral arterial disease; *PB-MNC,* peripheral blood-mononuclear cells; *$TcPO_2$,* transcutaneous partial pressure of oxygen; *VEGF,* vascular endothelial growth factor.

pleted by 92% at baseline, 61% at 3 months, and 52% at 12 months, and analysis showed that patients who did not complete the QOL assessment were more likely to have had an adverse event.

The BASIL trial evaluated heath-related QOL in 452 patients with CLI undergoing lower extremity bypass vs angioplasty.[21] The health-related QOL scores were similarly improved in both treatment arms, and with longer follow-up, there was a trend for improved health-related QOL in the surgery group, although this difference was not significant.

An interesting study by Seabrook et al[62] monitored CLI patients who had undergone successful vein bypass grafting for limb salvage for 6 months after arterial reconstruction. These patients were given a questionnaire based on the SF-36 that evaluated functional capacity and health-related QOL in these patients. This cohort was compared with a group of age- and gender-matched controls with normal limb pressures in the absence of occlusive vascular disease. Functional status was significantly worse in patients who had undergone arterial reconstruction, yet despite these functional limitations, the same group did not differ from controls in their perception of health and sense of well-being. Thus, even with successful graft patency and a perceived enhanced health-related QOL, these patients still face major functional limitations that must be factored into the overall assessment in treating patients with CLI.

Functional outcomes and QOL are pertinent issues that must be factored into the proper assessment and therapeutic choice for patients with CLI. Current data suggest these factors are improved in patients undergoing revascularization when patients live and ambulate independently preoperatively. When patients are not able to live or ambulate independently preoperatively, amputation may be superior to revascularization when assessing functional outcomes and QOL, although relevant level 1 data are lacking.

EMERGING THERAPIES

Exploring new strategies for revascularization in patients with CLI is of the utmost importance given (1) the large number of patients with CLI not eligible for revascularization procedures, (2) that amputation may confer an even worse prognosis, and (3) that medical management at this time is suboptimal. Currently, the goal of increasing or stimulating angiogenesis is being evaluated through clinical trials in patients with PAD and CLI (Table V).[63-69]

Gene therapy offers a potential efficacious therapy for patients with CLI, especially given that in the >1000 individuals treated with gene therapy for therapeutic angiogenesis in phase I and II trials, adverse events have been similar between treatment and control groups. Endothelial progenitor cells (EPC) derived from bone marrow or peripheral blood are another subset of emerging therapies implicated in the regeneration of injured endothelium and neoangiogensis after tissue ischemia and thus have been identified as a new potential therapeutic target in CLI.

Long-term safety data must be gathered before widespread use of these treatments can be adopted, given the theoretic potential for angiogenesis-triggered malignancies and the theoretic impact of angiogenesis on physiologic and pathologic processes, such as retinopathy and atherosclerotic plaque destabilization, although to date, preclinical and clinical experiences have not shown a manifestation of these processes.[70] Further, although both gene- and cell-based therapies in CLI seem promising in a subset of

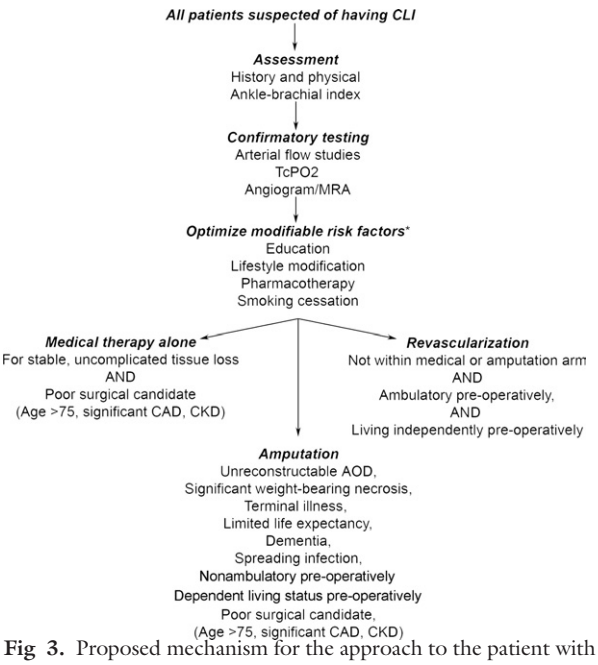

Fig 3. Proposed mechanism for the approach to the patient with critical limb ischemia *(CLI)*. *AOD,* Arterial occlusive disease; *CAD,* coronary artery disease; *CKD*, chronic kidney disease; *MRA*, magnetic resonance angiography; $TcPO_2$, transcutaneous partial pressure of oxygen.

patients, all of these studies to date lack adequate power as well as double-blinded controls. Also, other end points need to be examined in greater detail, including, for example, amputation rates and QOL, before a definite conclusion can be reached about the safety and efficacy of these novel therapies.

CONCLUSIONS

As outlined, CLI is a disease process with a tremendous cardiovascular burden. This makes the decision to perform a revascularization procedure vs amputation, or treat with medical therapy alone, a profoundly difficult one. Further, many CLI patients have significant comorbidities, including diabetes, renal disease, and advanced age, that further contribute to the overall morbidity and mortality in these patients. Revascularization, whether by surgical bypass or endovascular treatment, should be offered to patients with CLI if the procedure can be tolerated and the patient is ambulatory and living independently preoperatively. Amputation should be considered in those patients who are not ambulatory or living independently. Furthermore, a dedicated wound care program may alleviate sequela of CLI in select patients not amenable to surgical intervention.

Yet, the care of many patients with CLI is not straightforward, because multiple comorbidities increase operative risk significantly. Predictive indices may help the physician assess which patients may benefit from operative intervention on a more case-by-case basis. Further, in determining if operative management will cause more harm than good, the outcomes being assessed may be missing the "forest for the trees," and as more data on patient-focused outcomes are produced, we may change the way we treat patients with CLI. Much work in terms of randomized prospective studies needs to be done to validate if this is the case. Emerging therapies such as gene and cell-based therapies may hold promise in the future, but much research is still required.

In the meantime, we provide an algorithm for the evaluation and treatment of CLI, given the data generated during the last several years regarding medical and operative management in this patient population (Fig 3):

- We believe that patients with CLI able to perform independent activities of daily living without significant CAD or dialysis-dependent chronic kidney disease and age <75 years should be offered a revascularization procedure, by open or endovascular techniques.
- If these criteria are not met, or the CLI patient has limited life expectancy, dependent living situation, is nonambulatory preoperatively, has significant weight-bearing necrosis, or has spreading infection, then we believe primary amputation should be performed.
- If tissue loss is stable and uncomplicated, medical and wound therapy alone may be a viable option for poor surgical candidates; however, it must be kept in mind that these high-risk patients are victims to the limitations of surgical and medical management and potential for increased morbidity.

Given the medical and ethical dilemma that may arise when a physician is confronted with a patient with CLI, each patient must be examined on a case-by-case basis. Thus, this algorithm serves as a guide to be used in conjunction with the predictive indices presented while considering both physician-oriented and patient-oriented outcomes.

AUTHOR CONTRIBUTIONS

Conception and design: MK
Analysis and interpretation: VV, MH, MK
Data collection: VV, MH
Writing the article: VV, MH
Critical revision of the article: VV, MK
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Overall responsibility: MK

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